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Clinical Data Collection Methods in Molecular Medicine

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Clinical Data Collection in the Molecular Era

Evidenced-based medicine has been revolutionized by molecular biology, allowing for the development of deeper questions, more refined hypotheses, detailed diagnostics, targeted cellular processes, and more comprehensive data analyses. Yet, we have only begun to scratch the surface of how biomarkers and cellular activity affect diagnosis, treatment, and outcomes in most disease states. What we know about clinical data tied to molecular signatures comes through varying research methods. Data originates from interventional or real-world sources through a specific trial or data collection effort. Each are equipped to address specific sets of questions with associated strengths and weaknesses.

Clinical Data Collection Methods (Non-master Protocols)

The addition of molecular testing has provided more detail related to diagnosis, prognosis, and treatment of patients. However, it has not dramatically altered most trial designs. Interventional trials generally focus on determining how patients with a given biomarker identified by a specified test respond to a particular drug (i.e., one test, one biomarker, one treatment). Observational or chart review efforts can be used to identify potential molecularly based testing or treatment strategies but generally do not focus on a specific type of testing and rarely lead to a change in standard of care.

Interventional Master Protocols (Umbrella, Basket and Platform)

Master protocols address some of the challenges introduced by molecular medicine. Through shared infrastructure and screening methods, a more efficient data collection method is created. Like other interventional trials, the interventional master protocols generally focus on a specific treatment tied to a specific biomarker but have multiple adaptable arms (or disease histologies) running in a parallel fashion. (i.e., one or more tests with each linked to an associated biomarker, treatment, and study arm)

Real-world Master Observational Protocols

The master observational trial (MOT) is a new construct to bridge the gap that exists between the specificity of the interventional trials, and the broad nature of the actual practice of medicine. By hybridizing the scientific methods of the interventional trials with restricting data collection to the most clinically relevant elements, broader data collection can take place. Precise classification of molecular testing tied to longer-term outcomes across broad study populations allows for evaluation of higher complexity care models. The versatility of the MOT trial type allows for easy synergy with other trials and provides the flexibility of adding new elements or arms to address specific questions.

Pros and Cons

The quality of data tends to be proportional to the cost and complexity of collecting it. Investigational trials are the gold standard of evidence generation methods but are usually only used for drug development at only one point in time in a patients' treatment history. Real-world data efforts allow for much broader exploration, but the many drugs in many patients harboring many biomarkers approach can make finding an unbiased benefit challenging. Theoretically, questions regarding benefits of continually advancing molecular testing, of treating rare alterations or combinations of alterations, of sequencing or combining treatments, and of using treatments not approved by the FDA or specialty societies can be answered using real-world data sets. However, these answers require data of sufficient quality and quantity to mitigate bias. Lack of patient consent limits ability to reach back to a specific patient to verify benefits. In all trials of molecular medicine, interventional or real-world, there needs to be enough patients screened and enrolled to identify rare or complex associations and benefits.

Nuances and Linking of Methods

Table 1 shows the differences between typical trial types. Individual trials may employ additional methods to increase the quality and reliability of data. Any of these trial types can be used in parallel or sequence with other trial types, providing the ability to collect more robust information.

Challenges

We are beginning to understand the clinical implication of the foundational layer of molecular medicine: genomics. The deeper layers of transcriptomics, proteomics, metabolomics, epigenomics, cellular metabolism, microenvironment, host factors, immune factors, gut biome, and other factors steadily increase the complexity of clinical data collection. Ideally, we need to use every data collection method available to aggregate information on exponentially greater numbers of patients in order to truly understand personalized medicine.

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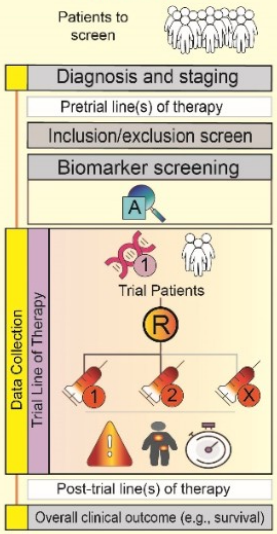
Legend:

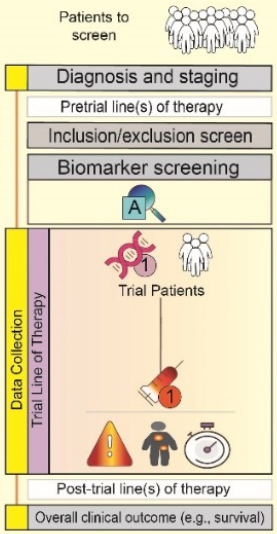
- **Biomarker testing method:** using a specific technology and instrument "A", "B", etc.
- **Biomarker testing method:** using any technology or instrument to find a biomarker
- **Specific biomarker(s) present:** any specific biomarker(s) tested and present; "1", "2", etc.
- **Specific biomarker(s) absent:** any biomarker(s) tested and not present
- **Randomization of patients**
- **Detailed toxicity:** determining side affects of a given treatment in a standardized fashion
- **Limited toxicity:** variable reporting of toxicity or limited toxicity data
- **Therapeutic intervention:** protocol-determined intervention: "1", "2", etc.
- **Standard intervention:** treatment determined by provider for given patient scenario: "1", "2", etc.
- **Response determination:** disease response quantified (e.g., overall response rate)
- **Response time:** time of disease responce to a treatment (e.g., progression free survival)
- **Data collection:** detailed clinical and related data (yellow box) and limited data collected (orange line)

Interventional Trials

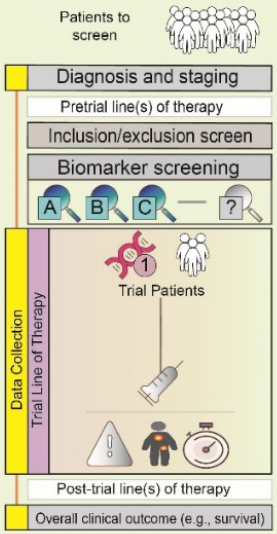
Randomized Controlled Trial



Single Arm Trial

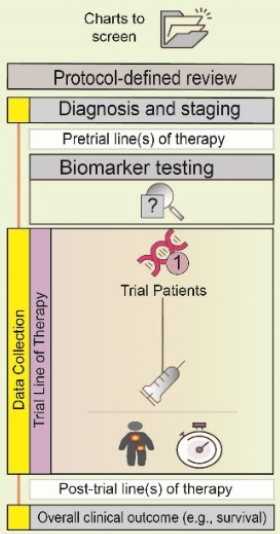


Prospective Observational Trial

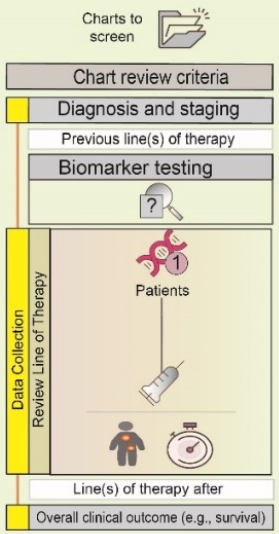


Real-world Data

Retrospective Observational Trial

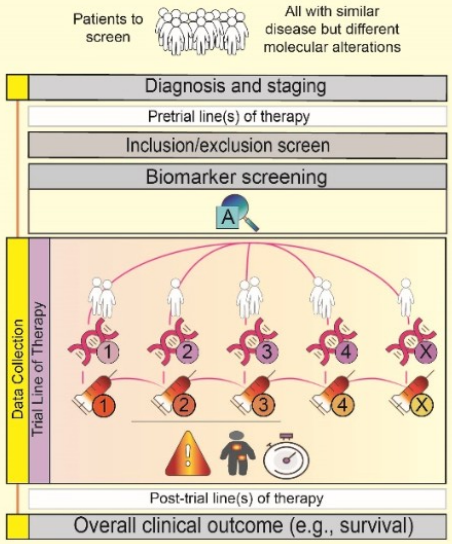


Medical Record Review

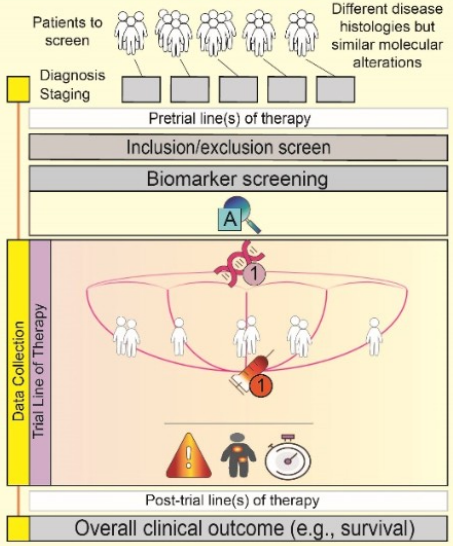


Master Interventional Trials

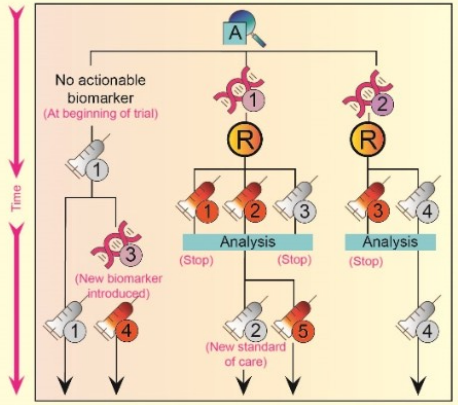
Umbrella Trial



Basket Trial



Platform Trial



Note: This is a hypothetical example of the organization and evolution of a platform trial. The master protocol governing the trial adds, removes, or replaces arms based on predetermined events such as pre-planned analysis or introduction of new interventions. Data collection generally focuses on the intervention and its associated outcome for the line of therapy and only limited information from pre and post-trial events.

Master Observational Trial